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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SZPERKA, MICHAEL EDWARD

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,135	KING ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that the examiner of record for your application has changed. To aid in paper matching, please address all future correspondence to Michael Szperka, Art Unit 1644, Technology Center 1600.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 7, 2006 has been entered.

Claims 1, 7, and 17 have been amended.

Claims 5, 6, and 20-35 are canceled.

Claims 1-4 and 7-19 are pending and under examination in the instant office action.

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Limitations concerning the length of peptide epitopes, such

as about 6 to about 45, about 6 to about 35, about 6 to about 25, and about 6 to about 15 are limitations discloses in claims 6-9 as originally filed, but these ranges do not appear to be disclosed within the text of the specification. Appropriate amendment of the specification is required.

The specification is also objected to for failing to comply with the Sequence Rules set forth in 37 CFR 1.821-1.825. Specifically, line 26 of page 50 contains a sequence not identified by a SEQ ID number, and numerous sequences appear in table 2 on page 51. Applicant is required to review the instant application for compliance with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825. Appropriate amendment of the specification is required in response to this action, and such an amendment may also potentiate the need for submission of a new sequence listing.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 and 7-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for allergen hybrid proteins of wasp antigen 5 wherein peptide epitopes greater than 8 amino acids in length obtained from a wasp

antigen 5 protein of one species are used to replace the corresponding peptide epitopes in a wasp antigen 5 protein of a different wasp species and the resulting hybrid molecule demonstrates reduced allergenicity but maintains immunogenicity and maintains the conformation present in a wild-type wasp antigen 5 protein, does not reasonably provide enablement for allergen hybrid proteins comprising peptide epitopes of about 6 to 45 amino acids of an allergen and a structurally homologous scaffold protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments filed 12/21/05 and entered 2/7/06 have been fully considered but they are not persuasive. Reconsideration of the claimed invention has also introduced additional issues not presented in the rejection of record. These new grounds of rejection as well as a response to applicant's arguments concerning the rejection of record will be addressed where appropriate below.

Applicant has claimed hybrid proteins that have reduced allergenicity but retained immunogenicity that comprise peptide epitopes and a scaffold protein structurally homologous to the allergen protein from which the peptide epitopes are obtained. These hybrid proteins are also recited as having the peptide epitope in a surface accessible region and as maintaining a native conformation. To support such a genus of hybrid proteins, applicant has provided examples wherein peptide epitopes from the antigen 5 protein of *Vespula vulgaris* are used to replace the corresponding positions in the *Polistes annularis* antigen 5 scaffold protein (see particularly examples 1-8 of the

instant specification). The rejection of record indicated that experimental data provided in applicant's specification demonstrates that a peptide epitope of 8 amino acids did not work in generating a functional hybrid protein (see particularly table 3B on page 56), that insertion of peptide fragments into scaffold proteins can lead to unpredictable destabilization of the conformation of the resulting molecule (the teachings of US2004/017116, of record, see entire document), and that hybrid proteins comprising 20-30 residues in the peptide epitope sequence have maximal reduction in allergenicity while still maintaining immunogenicity (King et al., J Immunology, 2001, 166:6057-6065, of record, see entire document, particularly the last sentence of the paragraph that spans pages 6064 and 6065). Applicant argues that the prior art enables peptides of about 6 amino acids because Harlow et al. (supplied by applicant and cited on the form 892 that accompanies this office action) teach that the smallest synthetic peptide that consistently elicits an antibody response is 6 amino acids, that the teachings concerning destabilization of polypeptide structure taught in the '116 publication are refuted by the evidence of the instant specification, and that the presence of an non-working example of an 8mer peptide epitope does not indicate that such small sequences (i.e. 8 or less) are inoperable given the four examples wherein epitopes of between 9 and 11 amino acids were used. The examiner respectfully disagrees.

Applicant begins by arguing that the claims are enabled for hybrid proteins comprising "about 6" amino acids. The specification does not appear to define what range of values are encompassed by the term "about", but it is reasonable that "about 6" includes sequences less than 6 amino acids. Based upon applicant's arguments and

the supplied Harlow et al. reference, epitopes under 6 amino acids are not expected to work and as such are not enabled. Further, Harlow et al. indicate that epitopes of 10 amino acids should be used as the lower limit for antibody production in the last sentence of the paragraph in which applicant's quotation appears (see page 76 of Harlow et al.) and King et al. teach that epitopes of 20-30 amino acids are preferred in the synthesis of hybrid allergen proteins. It is noted that applicant successfully generated a hybrid protein with the recited functional properties that comprised a 9 amino acid peptide epitope but a hybrid protein comprising an 8 amino acid epitope did not elicit an antibody response (see particularly table 3B on page 56). In light of the above, it appears clear that the claims are not enabled for peptide epitopes of "about 6" amino acids, especially since such a recitation reads on epitopes less than 6 amino acids.

B cell epitopes (i.e. those recognized by antibodies) come in two types, linear and discontinuous (Goldsby et al., Immunology, 5th edition 2003, pages 62-67, see entire selection). Discontinuous epitopes are made up of amino acids that are close together in the native tertiary structure of an antigen but are far apart in the primary amino acid sequence, and antibodies typically contact 15-22 amino acids in binding to an epitope (Goldsby et al., see particularly pages 63 and 64). It is known that the majority of B cell epitopes present on allergens are of the discontinuous type and that such epitopes depend on the native conformation of the protein (King et al., J Immunology, 2001, 166:6057-6065, of record, see entire document, particularly the second paragraph of the left column of page 6057 and the last sentence of the

paragraph that spans pages 6063 and 6064). As such, it appears that many of the peptide epitopes that applicant intends to include in the claimed hybrid proteins are linear determinants based upon their small size. On page 8 of the response filed 12/21/05 and entered 2/7/06 applicant states that he declines to characterize the peptide epitopes, saying that the recited peptide epitope may be a linear epitope, a conformational epitope, or some combination of linear and conformational epitopes. Since by definition discontinuous or conformational epitopes include amino acids widely separated in the primary amino acid sequence and since it is not reasonable that a 6 amino acid peptide includes widely separated amino acid residues, such epitopes are linear determinants. Applicant argues that the examiner's reliance on the '116 publication is misplaced since the instant specification refutes the general teaching that insertion of a linear peptide epitope from an insect allergen into an insect scaffold will destabilize the three-dimensional structure of the resulting molecule since the instant specification succeeds in doing what the '116 publication teaches will not work. However, the working examples of instant specification did not insert peptides into a scaffold protein such that the resulting molecule contains all of the sequence of the scaffold plus the inserted peptide thus making the hybrid protein larger than the starting scaffold, but rather applicant's invention involves swapping part of the scaffold protein with a peptide epitope from the same structural region of a related allergenic protein such that the overall length and structure of the hybrid protein as compared to the scaffold protein is not altered. Note that the claims as currently recited read on both inserting peptide epitopes to make longer hybrid proteins as well swapping peptide

epitopes of equivalent positions between an antigenic protein and a scaffold protein since a peptide epitope from a surface exposed loop of an allergen when either inserted or substituted into a surface exposed loop of the scaffold protein would make the peptide epitope surface exposed and in the same position, i.e. it would be in the surface exposed loop. Applicant argues that the recitation that the hybrid molecule has a native conformation is sufficient to address such an issue. However, as discussed above, insertion of peptides into a scaffold such that the length of the primary amino acid sequence is altered is unpredictable, and it is not clear if the "native conformation" is that of the allergen from which the peptide is isolated or the conformation of the scaffold protein. Such a discussion is relevant because since unless the two sequences are of equivalent length and sequence there must be at least some structural difference between the two polypeptides and it is not clear which structure needs to be maintained to meet the limitations of the claimed invention.

The specification does not appear to provide clear guidance as to what is required for a scaffold protein to be selected as "structurally homologous" to the allergen protein. The specification appears to suggest that structures solved by X-ray crystallography can be used, but guidance as to how similar two structures must be, such as percent deviation in the position of the Cα traces or other measures of structural similarity do not appear to be provided. For proteins for which no structure has been solved, applicant indicates that software for aligning sequences such as Pileup, Gap and BestFit can be used, but the parameters used by such software for comparison are not specified, and as such the criteria that are to be used in making the

determination of homology are uncertain. It is known in the art that amino acid sequence identity of 50% does not guarantee structural similarity (Yuan et al., Proteins, 1998, 30:136-143, see entire document), and that even a single point mutation in a polypeptide sequence can lead to surprising alterations in protein structure and activity (Sergel et al., J. Virol. 2000, 74:5101-5107, see entire document, particularly the abstract, introduction and the last sentence in the right column of page 5106). Given that the art recognizes difficulties in identifying structurally homologous proteins and the apparent lack of guidance in the specification concerning how a skilled artisan is to overcome these difficulties, it does not appear that applicant's working examples concerning the replacement of parts of antigen 5 of *P. annularis* with peptides from the corresponding position of antigen 5 of *V. vulgaris* convey to the claimed genus of all antigens and all scaffold proteins. Note that in applicant's working examples both wasp antigen 5 polypeptides are allergens, although allergic individuals generally, but not necessarily, have an IgE response directed to one but not both of these proteins. Structurally homologous proteins that can be used as scaffold proteins reasonably include endogenous self proteins which, except in autoimmunity, are not recognized by self antibodies, and as such it is unclear how immunogenicity would be maintained since it is not inherently present. Further, it is known that allergenicity cannot be determined *a priori* on a structural basis, and as such experimentation is required to ensure that the claimed hybrid peptides actually exhibit reduced allergenicity (Bumenthal et al., in Allergens and Allergen Immunotherapy, pages 37-50, see entire document, particularly the last sentence of the third full paragraph of page 39 and the

first sentence of the third full paragraph of page 42). Even when epitopes know to be important for binding to IgE have been identified, it is not predictable how changes to such sequence can result in removal of IgE binding and hence reduced allergenicity (Burks et al., Eur. J. Biochem, 1997, 245:334-339, see entire document, particularly the top right of page 338). It is also known that induction of an allergic response is a complicated process involving the interplay of diverse genetic and environmental factors that are not fully understood (Blumenthal et al., see entire document), and the relation of these factors are not further clarified by the teachings of the instant specification.

Therefore, based upon the breadth of applicant's claims, the evidence concerning the inoperability of small peptide sequences in applicant's claimed hybrid proteins especially those under 9 amino acids in length, the unpredictability of maintenance of structure in light of insertions and substitutions of amino acid sequences, the difficulty in identifying "homologous sequences" for use in the instant invention, and the unpredictability concerning diminution of IgE binding and therefore allergenicity, and all of the other factors discussed above, it appears that a skilled artisan would need to perform an undue amount of research in order to make and use the full breadth of applicant's claimed invention.

6. Claims 1-4, 7-13 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has broadly claimed hybrid proteins comprising peptide epitopes of an allergen and a scaffold protein. The identity of the allergen and scaffold can be anything in the broadest claims, are limited to wasp antigen 5 polypeptides in dependent claims, and applicant has made and gathered data concerning hybrid proteins comprising wasp antigen 5 sequences *V. vulgaris* and *P. annularis*. Some of the hybrid proteins made by applicant retain immunogenicity while exhibiting reduced allergenicity, while others do not (see particularly table 3B on page 56). It is known in the art that allergenicity, or a lack thereof, cannot be determined *a priori* on a structural basis (Bumenthal et al., in Allergens and Allergen Immunotherapy, pages 37-50, see entire document, particularly the last sentence of the third full paragraph of page 39 and the first sentence of the third full paragraph of page 42), and that even when epitopes know to be important for binding to IgE have been identified, it is not predictable how changes to such sequence can result in removal of IgE binding and hence reduced allergenicity (Burks et al., Eur. J. Biochem, 1997, 245:334-339, see entire document, particularly the top right of page 338). As such, there does not appear to be a core structure known in the art or disclosed in the specification that would allow a skilled artisan to know that a molecule has or does not have allergenicity due to the presence or absence of this core structure. The claims also recite that the scaffold protein and protein allergen are to be structurally homologous, but the specification does not appear to indicate what requirements must be met for a scaffold protein to be selected as

"structurally homologous" to the allergen protein. Solved X-ray crystal structures as well as computer-based sequence alignments are indicated as being useful tools in identifying homologous sequences, but the criteria to be used when implementing these tools does not appear to be disclosed. It is also known in the art that amino acid sequence identity of 50% does not guarantee structural similarity (Yuan et al., Proteins, 1998, 30:136-143, see entire document), and that even a single point mutation in a polypeptide sequence can lead to surprising alterations in protein structure and activity (Sergel et al., J. Virol. 2000, 74:5101-5107, see entire document, particularly the abstract, introduction and the last sentence in the right column of page 5106).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3). As discussed above, the correlation between structure and reduced allergenicity (i.e. decreased IgE binding) is not known in the art and does not appear to be taught in the instant specification. Further, the relevant structural features that are to be used in identifying "structurally homologous" proteins are not well defined. In light of this, one of

skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus of all allergen hybrid proteins. Thus, Applicant was not in possession of the claimed genus of all allergen hybrid proteins. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. The rejection of claims 1-4 and 10-17 under 35 U.S.C. 102(b) as being anticipated by Monsalve et al. (reference 1 on the 1/15/03 IDS) or Monsalve et al. (reference 7 on the 10/15/03 IDS) as evidenced by King et al. has been withdrawn in view of applicant's amendment of base claim 1 to remove the limitation "about" in the claim set submitted 12/21/05 and entered 2/7/06.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The rejection of claims 1, 18, and 19 under 35 U.S.C. 103(a) as being unpatentable over Monsalve et al. as evidenced by King et al. in view of US Patent 6,639,054 has been withdrawn in view of applicant's amendment of base claim 1 to introduce additional limitations not previously considered in the claim set submitted 12/21/05 and entered 2/7/06.

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 24, 2006

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